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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

4/L

Office Action Summary	Application No.	Applicant(s)	
	08/982,284	LUBON ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *111-116* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *111-116* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 12-17-04 has been entered.

The arguments filed 12-17-04 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-110 have been canceled. Claims 111-116 have been added. Claims 111-116 are pending and under consideration in the instant application.

The title of the application has been changed to "Compositions And Methods For Protein Expression In Transgenic Animal Urine". The title is not acceptable because no "compositions" are being claimed. The title should be changed to more closely reflect the scope of the claimed invention, i.e. Methods For Protein Expression In the Urine of Transgenic Mammals"

The effective filing date of the instant invention is 12-1-97.

Claim Objections

The claim objections have been withdrawn because the claims have been canceled.

Claim Rejections - 35 USC ' 112

New claims 111-116 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for reasons of record.

Claims 111-114 are currently limited to a method for secreting protein into urine, of a transgenic non-human mammal comprising:

a) providing;

i) a non-human mammal comprising a plurality of urinary tract cells;

ii) a nucleotide sequence encoding a protein operably linked to a promoter, wherein said promoter is selected from the group consisting of a whey acidic protein promoter, a uroplakin promoter, a uromodulin promoter, a uropontin promoter, an osteopontin promoter, a nephrocalcin promoter, and an aquaporin promoter;

b) introducing said nucleotide sequence into said urinary tract cells to create a transgenic non-human mammal',

c) expressing said protein in said urinary tract cells under conditions such that said protein is secreted into urine of said transgenic non-human mammal.

Claim 115 is directed toward a transgenic non-human mammal produced according to claim 111.

Claim 116 is directed toward urine of a transgenic non-human mammal produced according to claim 111.

The breadth of the claim has shifted as it relates to the promoters that allow expression and secretion of exogenous proteins in transgenic mammals.

Overall, it was unpredictable at the time of filing what effect a promoter would have on the phenotype of transgenic animals (Strojek, Houdebine, Wall and Kappel all of record).

Written description

Background: WAP and uroplakin promoters (currently claimed) capable of expressing and secreting exogenous protein in the urine of a transgenic non-human mammal have adequate written description

Lubon of record taught the WAP promoter allowed secretion of protein into the milk and urine of the transgenic mice and isolating the protein from the milk or urine (US Patent 5,880,327, March 9, 1999; col. 6, lines 45-52; col. 9, line 19). Sun of record taught the uroplakin promoter allowed secretion of protein into the urine of transgenic mice and using the bladder of the mice as a bioreactor for isolating the protein from the urine (WO 96/39494, Dec. 12, 1996; US Patent 5,824,543, Oct. 20, 1998; pg 8, lines 3-12; pg 9, lines 15-36; pg 10, line 4; ¶ bridging col. 5 and 6, col. 6, line 55, Example 2). The specification taught making transgenic mice and pigs whose genomes' comprised a sequence encoding human protein C (HPC) operatively linked to the WAP promoter, wherein said mice and pigs expressed HPC in their urine (¶ bridging pg 38-39). Thus, the specification provides adequate written description for the WAP and uroplakin

promoters as being capable of secreting exogenous proteins into the urine of transgenic mammals.

While the WAP and uroplakin promoters were described in the art as being capable of expressing and secreting exogenous proteins in the urine of transgenic mammals, neither the specification nor the art at the time of filing taught that expression of exogenous protein in the kidney or bladder of a transgenic meant that secretion into the urine would occur. Obtaining exogenous protein expression in the kidneys, urinary tract or reproductive tract does not correlate to secreting the exogenous protein in the urine as claimed because expression does not guarantee the protein is secreted out of the cell and into the urine. The exogenous protein may be expressed within a kidney or urinary tract cell, but the protein not have the proper signal sequence required to be secreted out of the cell, specifically into the urine. The proper promoter with adequate signal sequences that provide secretion into the urine must be in the transgene and control expression of the exogenous gene.

Background: The ApoE, Epo and renin promoters (not currently claimed) were known in the art at the time of filing and used to make transgenic non-human mammals. However, the specification and the art at the time of filing did not provide adequate written description that the ApoE, Epo or renin promoters were capable of expressing and secreting exogenous protein

Apolipoprotein E (not currently claimed)

Simonet of record (1990, J. Biol. Chem., Vol. 265, pages 10809-10812) taught transgenic mice whose genomes' comprise a transgene encoding a protein operatively linked to the apolipoprotein E promoter wherein expression of the protein occurs in the kidney (pg 10810, ¶ bridging col. 1-2) but did not teach mice secrete the protein into their urine. The specification suggests using an apoE promoter (pg 28, line 3, through pg 29, line 6) to express proteins in the kidney or bladder. The specification suggests making a construct for expression in the urinary tract with an ApoE promoter (pg 42, Example 3). The specification does not provide adequate written description for the apolipoprotein E 5' region required to secrete an exogenous protein into the urine of a transgenic mammal as claimed. The specification does not correlate the amount of expression obtained using WAP or uroplakin promoters to an ApoE promoter. The specification does not correlate the signal sequence of WAP or uroplakin 5' regulatory regions to ApoE regulatory regions. The teachings in the specification are, in fact, less than the teachings of Simone, who actually reduced the mouse to practice and did not teach obtaining secretion of exogenous protein into the urine. Therefore, the specification did not provide adequate description of the ApoE 5' regulatory regions required to secrete exogenous proteins into the urine of transgenic animals as claimed.

Renin (not currently claimed)

Fukamizu of record (Biochem. Biophys. Res. Comm., 1994, Vol. 199, pg 183-190) taught a mouse whose genome comprised a nucleic acid sequence comprising the chloramphenicol acetyl transferase (CAT) gene operably linked to a renin 5' regulatory

region but did not teach the mouse secreted CAT into its urine. While the specification suggests using a renin promoter (pg 28, line 3, through pg 29, line 6) to express proteins in the kidney or bladder, and one of skill could make a transgenic with a construct with the renin promoter, the specification does not provide adequate written description for the renin 5' regulatory region required to secrete an exogenous protein into the urine of a transgenic mammal as claimed. The specification does not correlate the amount of expression obtained using WAP or uroplakin promoters to a renin promoter. The specification does not correlate the signal sequence of WAP or uroplakin 5' regulatory regions to renin regulatory regions. The teachings in the specification are, in fact, less than the teachings of Fukamizu, who actually reduced the mouse to practice and did not teach obtaining secretion of exogenous protein into the urine. Therefore, the specification did not provide adequate description of the renin 5' regulatory regions required to secrete exogenous proteins into the urine of transgenic animals as claimed.

Since the time of filing, Germain of record (2001, Clin. Exp Pharm. Vol. 28, pg 1056-1059) taught using a rennin promoter to obtain protein expression in the kidney. However, the promoter was not known until 1998 (see pg 1056, col. 2, last sentence, reference 9, Germain). More importantly, Germain (2001) did not teach the rennin promoter caused secretion of the exogenous protein into the urine. Obtaining exogenous protein expression in the kidneys, urinary tract or reproductive tract is not adequate to show that secretion of the protein out of the cell and into the urine will occur. In the case of Germain (2001), the exogenous protein may have been expressed within the cells of the kidney without being secreted outside of the cells and

into the urine because the 5' regulatory region did not have the proper signal sequence required for secretion out of the cell, specifically into the urine.

Erythropoietin (not currently claimed)

Semenza of record (Annals NY Acad. Sci., 1994, Vol. 718, pg 41-49) taught a mouse whose genome comprised a nucleic acid sequence comprising the human erythropoietin gene, including the 5' and 3' regulatory regions. The protein was detected in the kidneys of the mice (pg 42, 2nd full ¶, Fig. 1, "Ki"). Haidar of record (J. Structural Biol. April 1997, Vol. 118, pg 220-225) taught a mouse whose genome comprised a nucleic acid sequence comprising the lacZ gene operably linked to the 5' and 3' erythropoietin regulatory region. The protein was detected in the kidneys of the mice (pg 222, last line). While the specification suggests using an Epo promoter (pg 28, line 3, through pg 29, line 6) to express proteins in the kidney or bladder, and one of skill could make a transgenic with a construct comprising the Epo promoter, the specification does not provide adequate written description for the Epo 5' regulatory region required to secrete an exogenous protein into the urine of a transgenic mammal as claimed. The specification does not correlate the amount of expression obtained using WAP or uroplakin promoters to an Epo promoter. The specification does not correlate the signal sequence of WAP or uroplakin 5' regulatory regions to Epo regulatory regions. The teachings in the specification are, in fact, less than the teachings of Semenza, who actually reduced the mouse to practice and did not teach obtaining secretion of exogenous protein into the urine. Therefore, the specification did

not provide adequate description of the Epo 5' regulatory regions required to secrete exogenous proteins into the urine of transgenic animals as claimed.

Rejection: Uromodulin, uropontin, osteopontin, nephrocalcin and aquaporin genes were known in the art, but the uromodulin, uropontin, osteopontin, nephrocalcin and aquaporin promoters (currently claimed) capable of expressing and secreting exogenous proteins into the urine of transgenic non-human mammals lack written description.

Uromodulin

Zbikowska of record (Biochem. J. 2002. Vol. 365. pg 7-11) taught using a 6.72 kb fragment of the uromodulin gene comprising the promoter and exons 1 and 2 to make mice that secreted exogenous proteins into their urine (pg 8, Fig. 1). Thus, the uromodulin gene fragment comprising the promoter and exons 1 and 2 was essential to obtaining secretion of exogenous protein into the urine. The specification suggests using a uromodulin promoter to express proteins in the kidney or bladder (pg 29, lines 26-27). The specification teaches isolating the human uromodulin promoter (pg 41, Example 2) and making a construct for expression in the urinary tract with a uromodulin promoter (pg 42, Example 3). The specification does not provide adequate written description for using a uromodulin 5' region to secrete an exogenous protein into the urine of a transgenic mammal because it does not teach that which is essential – the uromodulin gene fragment comprising the promoter and exons 1 and 2. While the human, rat and cow uromodulin promoters were described in Yu of record (1994, Gene

Expr., Vol. 4, pg 63-75), Yu did not teach the gene fragment that was essential to secrete exogenous proteins into the urine of transgenic mammals. The specification does not correlate the amount of expression obtained using WAP or uroplakin promoters to uromodulin promoters. The specification does not correlate the signal sequence of WAP or uroplakin 5' regulatory regions to uromodulin regulatory regions. Therefore, the specification does not provide adequate description of the uromodulin 5' regulatory region that caused protein secretion into the urine of transgenic animals as claimed.

Uropontin, osteopontin and aquaporin

While the specification suggests using a uropontin/osteopontin promoter (pg 28, line 3, through pg 29, line 6) to express proteins in the kidney or bladder, and one of skill could make a transgenic with a construct comprising the uropontin/osteopontin or aquaporin promoter, the specification does not provide adequate written description for the uropontin/osteopontin or aquaporin 5' regulatory regions required to secrete an exogenous protein into the urine of a transgenic mammal as claimed. The specification does not correlate the amount of expression obtained using WAP or uroplakin promoters to a uropontin/osteopontin or aquaporin promoter. The specification does not correlate the signal sequence of WAP or uroplakin 5' regulatory regions to uropontin/osteopontin or aquaporin regulatory regions. Therefore, the specification did not provide adequate description of the uropontin/osteopontin or aquaporin 5' regulatory regions required to secrete exogenous proteins into the urine of transgenic animals as claimed.

Since the time of filing Nelson of record (1998, Am J Physiol. Vol. 275. pg C216-226), Zharkikh of record (2002, Am J Physiol Renal Physiol. Vol. 283, pg F1351-1364) and Stricklett of record (1999, Exp Nephrol. Vol. 7, pg 67-74) made transgenic mammals comprising a nucleic acid sequence encoding a protein operably linked to an aquaporin 5' regulatory region; however, the fragment of the aquaporin 5' regulatory region used by Nelson, Zharkikh and Stricklett was not taught in the specification as originally filed. Nelson (1998) taught using a 14 kb 5' flanking region of the aquaporin 2 gene and references Hozawa of record (1996, Am Physiol Soc. Pg C1695-1702); however, Hozawa taught the aquaporin 2 promoter was variable (9 or 14 kb). One of ordinary skill would not have known to choose the 14 kb aquaporin 2 promoter of Hozawa. More importantly, Nelson, Zharkhik and Stricklett did not teach the aquaporin promoter caused secretion of the exogenous protein into the urine. Obtaining exogenous protein expression in the kidneys, urinary tract or reproductive tract is not adequate to show that secretion of the protein out of the cell and into the urine occurred. In the case of Nelson, Zharkhik and Stricklett, the exogenous protein may have been expressed within the cell without being secreted outside of the cell and into the urine because the 5' regulatory region did not have the proper signal sequence required to cause secretion out of the cell, specifically into the urine.

Likewise, Sakuma of record (2003, J Orthop Sci. Vol. 8, pg 361-366) made transgenic mammals comprising a nucleic acid sequence encoding a protein operably linked to a osteopontin 5' regulatory region; however, the fragment of the osteopontin 5' regulatory region used by Sakuma was not known in the art or taught in the

specification as originally filed. The osteopontin 5' regulatory region used by Sakuma was not available until 1998 (see pg 361, col. 2, "Production of Transgenic mice" reference 20; Sato). Applicants refer to Jiang (1998) in the arguments on pg 13 of the response filed 10-30-03; however, Jiang did not teach a transgenic mammal as claimed.

Nephrocalcin

Debois of record (J. Biol. Chem, 1994, Vol. 269, No. 2, pg 1183-1190) taught the mouse nephorcalcin gene was transcribed in mouse kidney and not in bone (pg 24, lines 1-5). The art at the time filing did not teach the mouse nephrocalcin promoter or secretory signal that allowed expression and secretion of exogenous protein into the urine of transgenic mammals. Since the time of filing, it does not appear that the nephrocalcin gene has been expressed in transgenic mammals. Nor has the nephrocalcin promoter been isolated and used in transgenic mammals.

Overall, an adequate written description of a uromodulin, uropontin, osteopontin nephrocalcin or aquaporin promoter (currently claimed) or an Epo, ApoE or renin promoter (currently not claimed) capable of expressing and secreting exogenous protein into the urine of a transgenic mammal as claimed requires more than a mere statement that it is part of the invention. It is not sufficient to state promoters from the uromodulin, uropontin, osteopontin, nephrocalcin or aquaporin genes are capable of secreting exogenous protein into the urine of transgenic mammals. A mere suggestion to use such promoters to secrete exogenous proteins into the urine of transgenic mammals in view of the unpredictability in the art of promoter function in transgenics is simply a wish

to know whether such promoters have that capability and to identify the secretory sequences of the gene required for secretion into the urine. Thus, claiming a method of expressing and secreting a protein into the urine of a mammal using any promoter of the uromodulin, uropontin, osteopontin, nephrocalcin or aquaporin gene (or Epo, ApoE or renin gene) without defining the specific structure of the promoter that has that function is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

Applicants argue the specification discloses the uromodulin promoter on pg 21, lines 3-19, the osteopontin promoter on pg 22, lines 5-12, the nephrocalcin promoter on pg 23, lines 24, through pg 24, line 4, and the aquaporin promoter on pg 22, line 5-12, and suggests using the uromodulin, osteopontin, nephrocalcin or aquaporin promoter to express and secrete exogenous proteins in the urine of transgenic mammals as claimed. Applicants conclude the uromodulin, osteopontin, nephrocalcin or aquaporin promoter will provide expression and secretion of exogenous protein in the urine of a transgenic mammal as claimed because the gene were known to be associated with urinary tract tissue. Applicants' argument is not persuasive.

Applicants' argument does not address the uropontin promoter as claimed, which remains rejected for reasons of record.

Listing possible promoters having a possible function as being capable of being used to secrete exogenous proteins in the urine of transgenic mammals is not adequate written description of the promoters. It is merely a wish to know promoters having such a function.

Applicants contemplate mice made using the renin, Epo and ApoE promoters are capable of secreting protein into their urine. Mice made with the renin, Epo and ApoE promoters were known in the art but were not known to have secreted proteins into their urine. Semenza of record taught a mouse whose genome comprised a nucleic acid sequence comprising the human erythropoietin gene, including the erythropoietin promoter. Haidar of record taught a mouse whose genome comprised a nucleic acid sequence comprising the lacZ gene operably linked to the Epo promoter. Simonet of record taught a mouse whose genome comprised a nucleic acid sequence comprising the ApoE promoter. Boyle of record taught a mouse whose genome comprised a nucleic acid sequence comprising the osteoprotegerin coding region operably linked to the apoE promoter. While the art taught at the time of filing taught transgenic mice made with the renin, ApoE and Epo promoter expressed exogenous protein in urinary tract cells, only the WAP and uroplakin promoter were known by those of skill to cause protein secretion into the urine of transgenic mammals as claimed.

Applicants have not shown the transgenic mice made using the renin, ApoE or Epo promoter known in the art secreted exogenous protein into their urine. Applicants have not provided adequate written description that transgenic mice expressing an exogenous protein in cells of their urinary tract will secret the exogenous protein into

their urine. Applicants have not shown that the renin, ApoE or Epo promoters had the appropriate signal sequence that would cause secretion into the urine as claimed or correlated structurally to the WAP or uroplakin promoters known to secrete protein into the urine of transgenics. Given the unpredictability of promoters that provide secretion of exogenous proteins into the urine of transgenic mammals of record, and a listing renin, ApoE or Epo promoters as possibly having the function of WAP and uroplakin, applicants do not overcome the unpredictability in the art so that one of skill would know that the renin, ApoE and Epo promoters would cause secretion of exogenous proteins in the urine of transgenics. Therefore, the renin, ApoE and Epo promoters were not adequately described in the specification or the art at the time of filing as being capable of expressing and secreting exogenous protein into the urine of a transgenic mammal.

For the same reasons, applicants have not shown that mice made using the uromodulin, osteopontin, uropontin, nephrocalcin or aquaporin promoter as currently claimed would secrete exogenous protein in their urine. Applicants have not provided adequate written description that mice expressing exogenous proteins in cells of the urinary tract will secret the exogenous protein into the urine. Applicants have not shown that the uromodulin, osteopontin, uropontin, nephrocalcin or aquaporin promoters had the appropriate signal sequence that would cause secretion into the urine as claimed or correlated structurally to the WAP or uroplakin promoters. Given the unpredictability of promoters that provide secretion of exogenous proteins into the urine of transgenic mammals of record, and a listing uromodulin, osteopontin, uropontin, nephrocalcin or aquaporin promoters as possibly having the function of WAP and uroplakin is

inadequate to overcome the unpredictability in the art. Therefore, the uromodulin, osteopontin, uropontin, nephrocalcin or aquaporin promoters were not adequately described in the specification or the art at the time of filing as being capable of expressing and secreting exogenous protein into the urine of a transgenic mammal.

The specification does not teach an assay to determine the parts of the uromodulin, osteopontin, uropontin, nephrocalcin or aquaporin (or renin, Epo, ApoE) promoters having the desired function. The level of expression obtained using the promoters claimed may be inadequate to obtain detectable levels of protein in the urine, the promoter may not function as expected in the transgenic and the tissue-specificity within the urinary tract may not be adequate to allow secretion into the urine. Therefore, the specification does not provide adequate written description for the uromodulin, osteopontin, uropontin, nephrocalcin or aquaporin promoters (or Epo, ApoE or renin promoters) that provide expression and secretion of exogenous protein in the urine of transgenic non-human mammals as claimed.

Applicants have argued in a previous response in the declaration by Dr. Serguei Soukharev, that protein expression in the urine of a transgenic mammal may be obtained using the uromodulin promoter (pg 9 of response filed 10-31-03). Therefore, applicants conclude the specification provides adequate written description for the promoter of the uromodulin gene that produces exogenous protein in the urine of transgenic mammals. Applicants' argument is not persuasive because the transgenic mammal was made using a construct comprising exons 1 and 2 (and it appears an intron) of the uromodulin 5' regulatory region, which was not described in the

specification or the art at the time of filing and is considered essential to the invention (see Exhibit 2A attached to the declaration filed 11-5-01). In fact, the declaration does not fully disclose what portion of the uromodulin 5' regulatory region was used because it says, "only part of uromodulin promoter is shown" (see caption of Exhibit 2A). Therefore, the declaration does not correlate to the specification as originally filed because it contains information that was not known at the time of filing or disclosed in the specification as originally filed. In addition, the declaration does not describe the structure of the uromodulin promoter required to produce exogenous protein in the urine of a transgenic mammal, which is essential to the invention.

The breadth of any uromodulin, osteopontin, etc. promoter as broadly claimed lacks written description

The specification and the art do not provide adequate written description for any uromodulin, osteopontin, nephrocalcin or aquaporin promoter as broadly claimed. i.e. "a" uromodulin promoter lacks written description because one uromodulin promoter does not describe all uromodulin genes. Applicants have not addressed this portion of the rejection.

3' Regulatory sequences that cause exogenous protein secretion into the urine of a transgenic mammal lack written description

This portion of the written description rejection has been withdrawn because the claims no longer require a 3' regulatory sequence.

Expressing and secreting enzymes in the urine of a transgenic mammal lacks adequate written description

Claim 114 is directed toward producing an enzyme in the urine of the transgenic mammal, which remains rejected under written description for reasons of record.

The specification does not provide adequate written description for any transgenics that express and secretes enzymes in their urine. While the specification teaches a number of enzymes in Fig. 7, expression of such enzymes in the urinary tract of a transgenic mammal may cause an alteration in the phenotype of the mammal. In addition, expression of such enzymes in the urinary tract of a transgenic mammal may cause the enzyme to be non-functional. The specification and the art at the time of filing do not teach transgenics expressing enzymes, specifically protease, glycosyltransferase, phosphorylase, kinase or γ-carboxylase, in the urine. Thus, the specification does not provide adequate written description that the combination of elements described have the desired function, i.e. the transgenics express functional enzyme in their urine or the enzyme alters the phenotype of the transgenic. Applicants have not addressed this aspect of the rejection.

New Matter

Claims 111-116 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Support for the enzymes of claim 114 are found in Fig. 7.

The specification as originally filed did not teach or suggest introducing the nucleotide sequence into the urinary tract cells to create a transgenic non-human mammal as broadly claimed in new claim 111. The claim encompasses injecting DNA into the urinary tract cells of an adult mammal (i.e. gene therapy) to make the mammal "transgenic," which is not contemplated in the specification as originally filed. The specification is limited to introducing a nucleic acid sequence encoding a protein operably linked to a promoter into the genome of the transgenic non-human mammal or providing a transgenic mammal whose genome comprises a nucleic acid sequence encoding a protein operably linked to a promoter.

The specification as originally filed does not contemplate the concept of "a plurality of urinary tract cells" in claim 111. Support for the concept has not been provided and none can be found in the specification as originally filed. Therefore, the phrase is new matter.

Support for the uropontin promoter in claim 111 has not been provided and none can be found in the specification as originally filed. Therefore, the uropontin promoter is new matter.

The limitation of "human" protein C in claim 112 is new matter.

A protein comprising "prothrombin, Factor VII... ...and albumin" in claim 113 is new matter because the phrase does not have support in the specification as originally filed.

A protein comprising "phytase, phosphate removing enzyme... ...and phenylacetaldehyde dehydrogenase" in claim 114 is new matter because the phrase does not have support in the specification as originally filed.

The concept of claiming the urine of a transgenic mammal as in claim 116 is new matter. Support for claiming the urine cannot be found in the specification as originally filed.

Enablement

Claims 111-116 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic non-human mammal whose genome comprises a transgene comprising a nucleic acid sequence encoding a protein operatively linked to a promoter that causes secretion of the protein into the urine of the transgenic mammal, wherein said protein is expressed and secreted into the urine of said transgenic non-human mammal and a method of producing a protein in the urine of said non-human mammal, does not reasonably provide enablement for using a uromodulin, uropontin, osteopontin, nephrocalcin or aquaporin promoter (or a renin, erythropoietin, or apolipoprotein E promoter) to obtain expression and secretion of exogenous protein in the urine of transgenic non-human mammals or expressing and secreting an enzyme in the urine of transgenic non-human mammals. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The specification does not enable expressing and secreting an exogenous protein into the urine of a transgenic non-human mammal using any uromodulin, uropontin, osteopontin, nephrocalcin or aquaporin promoter (currently claimed) or any Epo, ApoE or renin promoter (currently not claimed). The claims are not enabled because the uropontin, osteopontin, nephrocalcin, aquaporin, Epo, ApoE or renin promoter that provide secretion of a protein in the urine of the transgenic mammal are not adequately taught for the reasons set forth above in the written description rejection. Applicants' arguments have been addressed above in the written description rejection.

Claims 111-116 are not enabled because the specification does not provide adequate guidance for one of skill to make transgenic pigs, sheep, goats, cows, rabbits, or horses. ES cells that provide germline transmission in species other than mice had not been obtained. Furthermore, the parameters required to obtain germline transmission of an exogenous transgene differ between mammalian species for reasons of record. The art at the time the invention was made did not teach how to make a transgenic pig, sheep, goat, cow, rabbit or horse or how to obtain pig, sheep, goat, cow, rabbit or horse ES cells. Therefore, it was unpredictable how to make any transgenic non-human mammal as broadly claimed at the time the invention was made. The specification does not teach how to make a transgenic pig, sheep, goat, cow, rabbit or horse or how to obtain pig, sheep, goat, cow, rabbit or horse ES cells. Thus, it would

have required one of skill undue experimentation to determine how to make a transgenic non-human mammal as broadly claimed. Applicants have not addressed this issue.

The specification does not enable expressing enzymes in the urine of transgenic mammals (claim 114). The disclosed purpose of expressing enzymes in the urine of animals is to degrade/detoxify feces, urine, microbes or chemical pollutants. Sympson of record taught expressing stromelysin-1 (which degrades collagen) in transgenic mice and D'Armiento of record taught that transgenic mice expressing MMP (which also degrades collagen) do not survive (page 5734, col. 2, line 6). While the specification teaches a number of enzymes in Fig. 7, expression of such enzymes in the urinary tract of a transgenic mammal may cause an alteration in the phenotype of the mammal. In addition, expression of such enzymes in the urinary tract of a transgenic mammal may cause the enzyme to be non-functional. The specification and the art at the time of filing do not teach transgenics expressing enzymes, specifically protease, glycosyltransferase, phosphorylase, kinase or γ-carboxylase, in the urine. Given the purpose of the specification taken with the teachings in the specification and in the art, the specification does not enable expressing enzymes in the urine of a transgenic non-human animal. Applicants have not addressed this issue.

Applicants have argued the rejections under written description and enablement together. Such a response is improper because each rejection should be addressed separately in case the rejections should be appealed. Applicants may simply state the arguments for the enablement are the same as the arguments for the written description

rejection. Failure to separate the rejections in the arguments is improper. It is noted that applicants failed to address the enablement rejection regarding the breadth of transgenic non-human mammal and the rejection regarding expressing enzymes in the urine of transgenic mammals, which is also improper. Failure to address each of the rejections in future responses will be considered non-responsive. The instant office action has been issued merely to expedite prosecution.

Indefiniteness

Claims 111-116 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The previous rejections have been withdrawn because the claims have been canceled.

Claim 113 is indefinite because it is unclear how a protein can comprise "prothrombin, Factor VII... ... and albumin" as claimed.

Claim 114 is indefinite because it is unclear how a protein can comprise "phytase, phosphate removing enzyme... ...and phenylacetaldehyde dehydrogenase" as claimed.

Claim 115 is indefinite because the method of claim 111 is directed toward a method of secreting a protein into urine and is not directed toward the production of a transgenic non-human mammal.

Claim 116 is indefinite because the method of claim 111 is directed toward a method of secreting a protein into urine and is not directed toward the production of transgenic non-human mammal urine.

Claim Rejections - 35 USC § 102

The rejection of claims 75, 78, 79, 81, 82, 84, 87-89, 91, 92, 94, 95, 97, 100, 101 and 106 under 35 U.S.C. 102(b) as being anticipated by Fukamizu (Biochem. Biophys. Res. Comm., 1994, Vol. 199, pg 183-190) has been withdrawn because the claims have been canceled and because new claims 111-116 do not encompass using the renin promoter.

The rejection of claims 75, 78-83, 87-89, 91-96, 100, 102 and 107 under 35 U.S.C. 102(b) as being anticipated by Semenza (Annals NY Acad. Sci., 1994, Vol. 718, pg 41-49) has been withdrawn because the claims have been canceled and because new claims 111-116 do not encompass using the Epo promoter.

The rejection of claims 75, 78-83, 87-89, 91-96, 100, 102 and 107 under 35 U.S.C. 102(a) as being anticipated by Haidar (J. Structural Biol. April 1997, Vol. 118, pg 220-225) has been withdrawn because the claims have been canceled and because new claims 111-116 do not encompass using the Epo promoter.

The rejection of claims 75, 78-83, 87-89, 91-6, 100, 103 and 108 under 35 U.S.C. 102(b) as being anticipated by Simonet (J. Biological Chem., 1990, Vol. 265, pg 10809-10812) has been withdrawn because the claims have been canceled and because new claims 111-116 do not encompass using the ApoE promoter.

The rejection of claims 75, 78-82, 86-89, 91, 92, 94, 95, 99, 100, 103 and 108 under 35 U.S.C. 102(e) as being anticipated by Boyle (US Patent 6,613,544, Sept. 2, 2003) has been withdrawn because the claims have been canceled and because new claims 111-116 do not encompass using the ApoE promoter.

Claims 111, 113, 115 and 116 are rejected under 35 U.S.C. 102(b) as being anticipated by being anticipated by Yull (PNAS, 1995, Vol. 92, pg 10899-10903) as supported by Paleyanda of record (1994, Transgenic Res., Vol. 3, pg 335-343).

Yull taught a transgenic mouse whose genome comprised a sequence encoding Factor IX operatively linked to the WAP promoter. The WAP promoter caused expression of Factor IX in the milk. The WAP promoter inherently results in secretion of the protein in the urine of the mice as claimed because it has the same structure as the mouse described by applicants that secretes protein in its urine made using the WAP promoter, because the WAP promoter was known to cause expression in the kidney (Paleyanda, pg 338, ¶ bridging col. 1-2) and because Example 1 demonstrates the WAP promoter causes secretion of exogenous protein into the urine. Paleyanda supports the examiner's inherency argument and is not relied upon for the basis of the rejection. The mouse inherently produced urine as in claim 116.

Claims 111, 115 and 116 are rejected under 35 U.S.C. 102(b) as being anticipated by being anticipated by Nagasawa (Meiji Daigaku Nogakubu Kenkyu Hokoku, 1994, Vol. 100, pg 13-21) as supported by Paleyanda of record (1994, Transgenic Res., Vol. 3, pg 335-343).

Nagasawa taught a transgenic mouse whose genome comprised a sequence encoding human Growth Hormone operatively linked to the WAP promoter. The WAP promoter caused expression of human Growth hormone in the milk. The WAP promoter inherently results in secretion of the protein in the urine of the mice as claimed because it has the same structure as the mouse described by applicants that secretes protein in its urine made using the WAP promoter, because the WAP promoter was known to cause expression in the kidney (Paleyanda, pg 338, ¶ bridging col. 1-2) and because Example 1 demonstrates the WAP promoter causes secretion of exogenous protein into the urine. Paleyanda supports the examiner's inherency argument and is not relied upon for the basis of the rejection. The mouse inherently produced urine as in claim 116.

Claims 111, 113, 115 and 116 are rejected under 35 U.S.C. 102(b) as being anticipated by being anticipated by Niemann of record (Journal of Animal Breeding and Genetics, 1996, Vol. 113, No. 4-5, pg 437-444) as supported by Paleyanda of record (1994, Transgenic Res., Vol. 3, pg 335-343).

Niemann taught a transgenic mouse whose genome comprised a sequence encoding Factor VIII operatively linked to the WAP promoter. The WAP promoter caused expression of Factor VIII in the milk. The WAP promoter inherently results in secretion of the protein in the urine of the mice as claimed because it has the same structure as the mouse described by applicants that secretes protein in its urine made using the WAP promoter, because the WAP promoter was known to cause expression in the kidney (Paleyanda, pg 338, ¶ bridging col. 1-2) and because Example 1

demonstrates the WAP promoter causes secretion of exogenous protein into the urine. Paleyanda supports the examiner's inherency argument and is not relied upon for the basis of the rejection. The mouse inherently produced urine as in claim 116.

Claims 111, 115 and 116 are rejected under 35 U.S.C. 102(b) as being anticipated by being anticipated by Sympson of record (May 1994, J. Cell Biol., Vol. 125, 681-693) for reasons of record in the office action sent 6-25-01, pg 18, as supported by Paleyanda of record (1994, Transgenic Res., Vol. 3, pg 335-343).

Sympson taught a transgenic mouse whose genome comprised a sequence encoding stromelysin-I operatively linked to the WAP promoter (page 683, col. 1, 1st ¶). The WAP promoter caused expression of the protein in the milk (¶ bridging pg 683-684). The WAP promoter inherently results in secretion of the protein in the urine of the mice as claimed because the WAP promoter was known to cause expression in the kidney (Paleyanda, pg 338, ¶ bridging col. 1-2) and because Example 1 demonstrates the WAP promoter causes secretion of exogenous protein into the urine. Paleyanda supports the examiner's inherency argument and is not relied upon for the basis of the rejection. The mouse inherently produced urine as in claim 116.

Claims 111, 115 and 116 are rejected under 35 U.S.C. 102(a) as being anticipated by Sun of record (WO 96/93494, Dec. 12, 1996) or 102(e) as being anticipated by Sun of record (US Patent 5,824,543, Oct. 20, 1990) for reasons of record (see office action sent 6-25-01, pg 19).

Sun taught transgenic mice whose genomes' comprised a sequence encoding β-galactosidase operatively linked to the uroplakin promoter and obtaining expression of

β-galactosidase in the urine and isolating the protein from the urine (W0 96/93494 – pg 8, lines 3-12; pg 9, lines 15-36; pg 10, line 4; ¶ bridging col. 5 and 6, col. 6, line 55, Example 2; US Patent 5,824,543 - col. 6, lines 5 and 55). The mice inherently produced urine as in claim 116.

Claims 111, 112, 115 and 116 are rejected under 35 U.S.C. 102(b) as being anticipated by Paleyanda of record (Transgenic Res., 1994, Vol. 3, pg 334-343).

Paleyanda taught making a mouse whose genome comprised a nucleic acid sequence encoding the human protein C operably linked to the WAP promoter. The human protein C was secreted into the milk of the mice. The human protein C was inherently secreted into the urine of the mouse because it was expressed in the kidney (pg 338, ¶ bridging col. 1-2) and because Example 1 demonstrates the WAP promoter causes secretion of exogenous protein into the urine. The mouse inherently produced urine as in claim 116.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER